193

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re application of:
BIRNSTIEL *et al.*
Appl. No. 08/380,200
Filed: January 30, 1995
For: **New Protein-Polycation Conjugates**

Art Unit: 1644
Examiner: Eisenschenk, F.
Atty. Docket: 0652.1080001/RWE

#36
B.G.J
5/15/99

Brief on Appeal to the Board of Patent Appeals and Interferences Under 37 C.F.R. § 1.192

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This is an Appeal from the final rejection of claims 1-20, 28, 29, 32-34 and 36-40 for the above-captioned U.S. patent application, for which a Notice of Appeal was filed on February 10, 1999. Appellants hereby file their appeal brief in triplicate as required under 37 C.F.R. § 1.192(a). Appellants also file herewith the fees as set forth in 37 C.F.R. § 1.17(c).

Real Party in Interest (37 C.F.R. § 1.192(c)(1))

The real parties in interest in this matter are Boehringer Ingelheim International GmbH and Genentech, Inc., assignees of record of all right, title and interest in the above-captioned application, as demonstrated by the Assignment recorded at reel 6582, frame 0138.

Related Appeals and Interferences (37 C.F.R. § 1.192(c)(2))

Appellants, including the undersigned legal representative and the assignees of the above-captioned application, are aware of no pending appeal or interference which will directly affect, be affected by or have bearing on the decision by the Board of Patent Appeals and Interferences ["the Board"] in the pending appeal.

Status of Claims (37 C.F.R. § 1.192(c)(3))

The above-captioned application was filed with claims 1-40 on January 30, 1995, as a Rule 62 continuation of Application No. 07/946,498, filed November 9, 1992, now abandoned.

In the Preliminary Amendment filed November 9, 1992, Appellants amended claims 8, 9, 15, 16, 18-20, 28, 30, 32 and 35-38.

In the Preliminary Amendment filed August 16, 1993, Appellants added claims 39 and 40.

In the Office Action of September 14, 1993 (Paper No. 7), the Examiner set forth a restriction requirement and withdrew claims 21-27, 30, 31 and 35 from consideration, and provisionally rejected claims 1-20, 28, 29, 32-34 and 36-40 under the judicially created doctrine of obviousness-type double patenting, rejected claims 1-20, 28, 29, 32-34 and 36-40 under 35 U.S.C. § 101 and objected to the specification and rejected claims 1-20, 28, 29, 32-34 and 36-40 under 35 U.S.C. § 112, first paragraph. In addition, the Examiner rejected claims 1, 6, 11, 13-18, 36 and 38 under 35 U.S.C. § 102(b) and rejected claims 2-5, 7-10, 12, 28, 29, 32-34, 37, 39 and 40 under 35 U.S.C. § 103. The Examiner set forth two rejections under 35 U.S.C. § 103 rejecting

claims 2-5, 7-10, 12, 37, 39 and 40 in the first rejection and claims 28, 29 and 32-34 in the second rejection.

Appellants responded to the Office Action on March 11, 1994, and amended claim 1.

In the final Office Action of May 31, 1994 (Paper No. 10), the Examiner maintained the provisional rejection of claims 1-20, 28, 29, 32-34 and 36-40 under the judicially created doctrine of obviousness-type double patenting, the rejection of claims 1-20, 28, 29, 32-34 and 36-40 under 35 U.S.C. § 101 and the objection to the specification and rejection of claims 1-20, 28, 29, 32-34 and 36-40 under 35 U.S.C. § 112, first paragraph. In addition, the Examiner maintained the rejection of claims 17, 18, 36 and 38 under 35 U.S.C. § 102(b) and the rejection of claims 2-5, 7-10, 12, 28, 29, 32-34, 37, 39 and 40 under 35 U.S.C. § 103. The Examiner set forth one new rejection under 35 U.S.C. § 103 rejecting claims 1, 3-7 and 11-16. The Examiner withdrew the rejection of claims 1, 6, 11 and 13-16 under 35 U.S.C. § 102(b).

Appellants responded to the Office Action on November 29, 1994, and amended claim 17.

In the Advisory Action of December 22, 1994 (Paper No. 14), the Examiner indicated that the amendment would not be entered and that claims 1-20, 28, 29, 32-34 and 36-40 remained rejected.

On January 30, 1995, Appellants requested a Rule 62 continuation application and entry of the amendment filed on November 29, 1994.

In the Office Action of February 28, 1996 (Paper No. 18), the Examiner maintained the provisional rejection of claims 1-20, 28, 29, 32-34 and 36-40 under the judicially created doctrine of obviousness-type double patenting and the objection to the specification and rejection of claim 38 under 35 U.S.C. § 112, first paragraph. The Examiner withdrew the rejection of claims 1-20, 28, 29, 32-34 and 36-40 under 35 U.S.C. § 101, the rejection of claims 1-20, 28, 29, 32-34, 36,

37, 39 and 40 under 35 U.S.C. § 112, first paragraph, and the rejection of claims 17, 18, 36 and 38 under 35 U.S.C. § 102(b). The Examiner presented three rejections under 35 U.S.C. § 103 rejecting claims 1-8, 11-20 and 36-40 in the first rejection, claims 17, 20, 28, 29 and 32-34 in the second rejection and claims 1, 9 and 10 in the third rejection. Claims 21-27, 30, 31 and 35 remained withdrawn from consideration based on the election in response to the restriction requirement presented in the parent application, 07/946,498.

Appellants responded to the Office Action on August 28, 1996.

In the final Office Action of December 24, 1996 (Paper No. 22), the provisional rejection of claims 1-20, 28, 29, 32-34 and 36-40 under the judicially created doctrine of obviousness-type double patenting and the objection to the specification and rejection of claim 38 under 35 U.S.C. § 112, first paragraph, were withdrawn. The rejections under 35 U.S.C. § 103 were maintained.

Appellants responded to the Office Action on May 27, 1997.

The Advisory Action of June 23, 1997 (Paper No. 25), indicated that the rejections under 35 U.S.C. § 103 were maintained.

On August 12, 1997, Appellants requested that the finality of the December 24, 1996, Office Action be withdrawn and the response filed May 27, 1997, be entered under 37 C.F.R. § 1.129(a).

In the Office Action of October 28, 1997 (Paper No. 29), the Examiner maintained the rejections of claims 1-20, 28, 29, 32-34 and 36-40 under 35 U.S.C. § 103.

Appellants responded to the Office Action on April 27, 1998.

In the final Office Action of August 13, 1998 (Paper No. 31), the Examiner maintained the rejections of claims 1-20, 28, 29, 32-34 and 36-40 under 35 U.S.C. § 103.

The claims currently on appeal are claims 1-20, 28, 29, 32-34 and 36-40 (set forth in the Appendix of the Claims), each of which stands rejected under 35 U.S.C. § 103.

Appellants submit herewith an Amendment Under 37 C.F.R. § 1.116. This amendment cancels claim 34 which is nearly identical to claim 33.

Status of Amendments (37 C.F.R. § 1.192(c)(4))

The amendments filed November 9, 1992, August 16, 1993, March 11, 1994 and November 29, 1994, have been entered. The amendment filed herewith has not yet been entered.

Summary of the Invention (37 C.F.R. § 1.192(c)(5))

The claimed invention is drawn to protein-polycation conjugates and protein-polycation conjugates bound to nucleic acids or nucleic acid analogues to form complexes. The complexes are internalized into cells which express a T-cell surface protein. The protein component of the conjugates is a protein that binds to a T-cell surface protein other than the transferrin receptor. Possible proteins include a monoclonal antibody or fragment thereof directed against a T-cell surface protein; protein that binds to CD4 or CD7; anti-CD4 monoclonal antibody or fragment thereof containing a gp120 binding epitope; anti-CD3 monoclonal antibody; HIV-1 gp120, homologous protein of a related retrovirus or CD4 binding fragment of a homologous protein of a related retrovirus; or protein that binds to a tumor marker expressed on T-cells. Possible polycations include protamine, modified protamine, histone, modified histone, synthetic

polypeptides such as polylysine and polycations with about 20 to 500 positive charges. Possible nucleic acids include virus-inhibiting and oncogene-inhibiting nucleic acids.

Additional embodiments of the claims are drawn to conjugates wherein the protein component is an antibody bound to protein A which is coupled to the polycation, protein A-polycation conjugates and complexes that contain an additional polycation.

Another embodiment is drawn to processes for introducing nucleic acids into cells that express a T-cell surface protein using the protein-polycation conjugates and complexes described above.

Another embodiment is drawn to protein-polycation conjugates bound to nucleic acids wherein the nucleic acid is a virus-inhibiting or oncogene-inhibiting nucleic acid in the form of a ribozyme or a virus-inhibiting nucleic acid in the form of a genetic unit containing a tRNA-gene as a carrier and a ribozyme gene.

Another embodiment is drawn to pharmaceutical preparations containing the protein-polycation-nucleic acid complexes described above wherein the nucleic acid is therapeutically active or gene therapeutically active.

Issues (37 C.F.R. § 1.192(c)(6))

A. Are claims 1, 2, 8, 11-18 and 36, which are directed to protein-polycation conjugates and, more specifically, antibody-polycation conjugates or antibody fragment-polycation conjugates, which are capable of forming soluble complexes with nucleic acids or nucleic acid analogues and the complexes thereof which are absorbed into T-cells, as well as to processes for introducing nucleic acids into cells which express T-cell surface proteins using the

complexes, rendered obvious over prior art references which disclose asialoglycoprotein-, transferrin-, hormone- and antibody-polycation conjugates that form complexes with DNA and are absorbed into cells, where there is no suggestion to bind a protein, which is capable of binding to a cell surface protein of T-cell lineage, to a polycation for absorption into T-cells?

B. Is claim 3, which is directed to CD4-binding protein-polycation conjugates which are capable of binding to CD4 and forming soluble complexes with nucleic acids or nucleic acid analogues which are absorbed into T-cells, rendered obvious over prior art references which disclose asialoglycoprotein-, transferrin-, hormone- and antibody-polycation conjugates that form complexes with DNA and are absorbed into cells, where there is no suggestion to bind a CD4-binding protein to a polycation for absorption into T-cells?

C. Is claim 4, which is directed to conjugates containing a polycation bound to an anti-CD4 monoclonal antibody or conjugates containing a polycation bound to an anti-CD4 monoclonal antibody fragment containing a gp120 binding epitope which are capable of forming soluble complexes with nucleic acids or nucleic acid analogues which are absorbed into T-cells, rendered obvious over prior art references which disclose asialoglycoprotein-, transferrin-, hormone- and antibody-polycation conjugates that form complexes with DNA and are absorbed into cells, where there is no suggestion to bind an anti-CD4 antibody monoclonal or anti-CD4 monoclonal antibody fragment containing a gp120 binding epitope to a polycation for absorption into T-cells?

D. Is claim 5, which is directed to conjugates containing a polycation bound to HIV-1 gp120, conjugates containing a polycation bound to an HIV-1 gp120 homologous protein of a related retrovirus or conjugates containing a polycation bound to a CD4-binding fragment of an HIV-1 gp120 homologous protein of a related retrovirus, which are capable of forming soluble

complexes with nucleic acids or nucleic acid analogues which are absorbed into T-cells, rendered obvious over prior art references which disclose asialoglycoprotein-, transferrin-, hormone- and antibody-polycation conjugates that form complexes with DNA and are absorbed into cells, where there is no suggestion to bind HIV-1 gp120, a homologous protein of a related retrovirus or a CD4-binding protein fragment thereof to a polycation for absorption into T-cells?

E. Is claim 6, which is directed to protein-polycation conjugates wherein the protein binds to a tumor marker expressed on T-cells, which are capable of forming soluble complexes with nucleic acids or nucleic acid analogues which are absorbed into T-cells, rendered obvious over prior art references which disclose asialoglycoprotein-, transferrin-, hormone- and antibody-polycation conjugates that form complexes with DNA and are absorbed into cells, where there is no suggestion to bind a tumor marker-binding protein to a polycation for absorption into T-cells?

F. Is claim 7, which is directed to CD7-binding protein-polycation conjugates, which are capable of forming soluble complexes with nucleic acids or nucleic acid analogues which are absorbed into T-cells, rendered obvious over prior art references which disclose asialoglycoprotein-, transferrin-, hormone- and antibody-polycation conjugates that form complexes with DNA and are absorbed into cells, where there is no suggestion to bind a CD7-binding protein to a polycation for absorption into T-cells?

G. Is claim 19, which is directed to complexes comprising protein-polycation conjugates bound to nucleic acids, wherein the complexes contain an additional non-covalently bound polycation and are absorbed into T-cells, rendered obvious over prior art references which disclose asialoglycoprotein-, transferrin-, hormone- and antibody-polycation conjugates that form

complexes with DNA and are absorbed into cells, where there is no suggestion to bind a second polycation to the complex?

H. Is claim 20, which is directed to complexes comprising protein-polycation conjugates bound to virus-inhibiting nucleic acids, which are absorbed into T-cells, rendered obvious over prior art references which disclose asialoglycoprotein-, transferrin-, hormone- and antibody-polycation conjugates that form complexes with DNA and are absorbed into cells, where there is no suggestion to bind a virus-inhibiting nucleic acid to a protein-polycation conjugate for absorption into T-cells?

I. Is claim 37, which is directed to a process for introducing nucleic acids into T-cells wherein antibody-protein A-protamine-virus-inhibiting nucleic acid complexes are absorbed into T-cells, rendered obvious over prior art references which disclose asialoglycoprotein-, transferrin-, hormone- and antibody-polycation conjugates that form complexes with DNA and are absorbed into cells, where there is no suggestion to combine an antibody, protein A, protamine and a virus-inhibiting nucleic acid for absorption into T-cells?

J. Is claim 38, which is directed to pharmaceutical preparations containing protein-polycation conjugates bound to therapeutically or gene therapeutically active nucleic acids to form complexes which are absorbed into T-cells, rendered obvious over prior art references which disclose asialoglycoprotein-, transferrin-, hormone- and antibody-polycation conjugates that form complexes with DNA and are absorbed into cells, where there is no suggestion to bind a therapeutically or gene therapeutically active nucleic acid to a protein-polycation conjugate for absorption into T-cells?

K. Are claims 39 and 40, which are directed to anti-CD3 monoclonal antibody-polycation conjugates (claim 39) which are capable of forming soluble complexes with nucleic

acids or nucleic acid analogues, and the complexes thereof (claim 40), which are absorbed into T-cells, rendered obvious over prior art references which disclose asialoglycoprotein-, transferrin-, hormone- and antibody-polycation conjugates that form complexes with DNA and are absorbed into cells, where there is no suggestion to bind an anti-CD3 monoclonal antibody to a polycation for absorption into T-cells?

L. Is claim 28, which is directed to complexes comprising protein-polycation conjugates bound to virus-inhibiting nucleic acids in the form of ribozymes, which are absorbed into T-cells, rendered obvious over prior art references which disclose asialoglycoprotein-, transferrin-, hormone- and antibody-polycation conjugates that form complexes with DNA and are absorbed into cells and which disclose that ribozymes are known, where there is no suggestion to bind a ribozyme to a protein-polycation conjugate for absorption into T-cells?

M. Is claim 29, which is directed to complexes comprising protein-polycation conjugates bound to virus-inhibiting nucleic acids in the form of genetic units consisting of tRNA-genes as carrier genes and ribozyme genes, which are absorbed into T-cells, rendered obvious over prior art references which disclose asialoglycoprotein-, transferrin-, hormone- and antibody-polycation conjugates that form complexes with DNA and are absorbed into cells and which disclose that ribozymes are known, where there is no suggestion to bind the genetic unit to a protein-polycation conjugate for absorption into T-cells?

N. Is claim 32, which is directed to complexes comprising protein-polycation conjugates bound to oncogene-inhibiting nucleic acids, which are absorbed into T-cells, rendered obvious over prior art references which disclose asialoglycoprotein-, transferrin-, hormone- and antibody-polycation conjugates that form complexes with DNA and are absorbed into cells, where

there is no suggestion to bind an oncogene-inhibiting nucleic acid to a protein-polycation conjugate for absorption into T-cells?

O. Are claims 33 and 34, which are directed to complexes comprising protein-polycation conjugates bound to oncogene-inhibiting nucleic acids in the form of ribozymes, which are absorbed into T-cells, rendered obvious over prior art references which disclose asialoglycoprotein-, transferrin-, hormone- and antibody-polycation conjugates that form complexes with DNA and are absorbed into cells and which disclose that ribozymes are known, where there is no suggestion to bind a ribozyme to a protein-polycation conjugate for absorption into T-cells?

P. Is claim 9, which is directed to antibody-protein A-polycation conjugates which are capable of forming soluble complexes with nucleic acid or nucleic acid analogues which are absorbed into T-cells, rendered obvious over prior art references which disclose asialoglycoprotein-, transferrin-, hormone- and antibody-polycation conjugates that form complexes with DNA and are absorbed into cells and which disclose that protein A is known, where there is no suggestion to bind an antibody-protein A complex to a polycation for absorption into T-cells?

Q. Is claim 10, which is directed to protein A-polycation conjugates which may be used to prepare antibody-protein A-polycation conjugates which are capable of forming soluble complexes with nucleic acid or nucleic acid analogues which are absorbed into T-cells, rendered obvious over prior art references which disclose asialoglycoprotein-, transferrin-, hormone- and antibody-polycation conjugates that form complexes with DNA and are absorbed into cells and which disclose that protein A is known, where there is no suggestion to bind protein A to a polycation?

Grouping of Claims (37 C.F.R. § 1.192(c)(7))

For purposes of this appeal, all of the claims do not stand or fall together.

Group I: Claims 1, 2, 8, 11-18 and 36.

Group II: Claim 3.

Group III: Claim 4.

Group IV: Claim 5.

Group V: Claim 6.

Group VI: Claim 7.

Group VII: Claim 9.

Group VIII: Claim 10.

Group IX: Claim 19.

Group X: Claim 20.

Group XI: Claim 28.

Group XII: Claim 29.

Group XIII: Claim 32.

Group XIV: Claims 33 and 34.

Group XV: Claim 37.

Group XVI: Claim 38.

Group XVII: Claims 39 and 40.

The claims have been grouped separately since each group involves different conjugate and complex components and, therefore, presents different legal issues.

Arguments (37 C.F.R. § 1.192(c)(8))

I. Rejection of claims 1-8, 11-20 and 36-40 under 35 U.S.C. § 103

A. Examiner's Statement of Rejection

The Examiner has maintained the rejection of claims 1-8, 11-20 and 36-40 under 35 U.S.C. § 103. Specifically, the Examiner set forth the rejection as follows:

> Claims 1-8, 11-20, and 36-40 stand rejected under 35 U.S.C. § 103 as being unpatentable over Wu et al. (AC1) or Wagner et al. (AT2) in view of Goers et al. or Hirsch et al. ('132), Carriere et al., Knapp et al., and Young et al. (J. Immunol., 136:4700) or Weinberger et al. (J. Cell Biochem.).

Paper No. 31, page 2, lines 9-12.

According to the Examiner, Wu *et al.* teach transfection of hepatocytes using asialoprotein-polycation conjugates. The polycation can be, *inter alia*, polylysine or a histone. In addition, according to the Examiner, Wu *et al.* indicate that instead of an asialoprotein, a hormone or an antibody may be used to direct the polycation conjugate to the target cell.

Regarding the alternative primary reference, Wagner *et al.*, the Examiner states that the reference teaches a method of transfecting cells with DNA using a transferrin-polycation conjugate. The polycation can be, *inter alia*, polylysine or protamine.

The Examiner states that the "references do not teach the use of T-cell specific antibodies for the targeting of polycation-nucleic acid complexes into cells." Paper No. 31, page 2, lines 9-12.

In an attempt to cite a reference which allegedly teaches the use of T-cell specific antibodies in the context of the claimed invention, the Examiner cites Goers *et al.* and Hirsch *et al.*, in the alternative.

The Examiner states that Goers *et al.* teach that, "therapeutic agents are selected for their intended application." Paper No. 31, page 2, line 30. From this assessment, the Examiner concludes that if one skilled in the art were to target T-cells, then one skilled in the art would select antibodies specific for T-cell antigens.

The Examiner states that Hirsch *et al.* teach that T-cell specific antibody-DNA conjugates are known and further, that Hirsch *et al.* teach the use of T-cell specific antibodies to target T-cells to produce interleukins or for conducting transformations.

Next, the Examiner cites Carriere *et al.* for the proposition that cells which express CD4, CD5 and CD7 receptors internalize anti-CD4, -CD5 and -CD7 antibody-conjugates. The Examiner further asserts that Appellants have admitted that CD7 is a tumor associated antigen.

Based on Wu *et al.* or Wagner *et al.* in view of Goers *et al.* or Hirsch *et al.* and Carriere *et al.*, the Examiner concludes that:

> The substitution of such antibodies as targeting agents of protein-polycation complexes would have ben [sic] obvious to one of ordinary skill where the targeting of [a] T-cell was desired. . . . The use of gp120 to target polycation-nucleic acid complexes to CD4 expressing cells would be functionally analogous to using anti-CD4 antibodies, and in view of the state of the art at the time of invention, an obvious means of targeting therapeutic agents to CD4 expressing cells in view of the state of the art and the recognition in the art that the HIV virus was internalized into CD4 expressing cells through the interaction of gp120 with the CD4 molecule.

Paper No. 31, page 2, last line, through page 3, line 10.

Next, the Examiner describes Zon *et al.* (cited in the specification at page 18) which is not cited in the statement of rejection. The Examiner asserts that Zon *et al.* teach various methods

of making nucleic acid analogues and further, that nucleic acid analogues are used to treat HIV infections.

The Examiner then cites Young *et al.* and Weinberger *et al.* which allegedly teach that the expression of interferon or a differentiation antigen may be obtained by transfecting T-cells with γ-interferon or a differentiation antigen encoding DNA. According to the Examiner, these two references demonstrate that "one skilled in the art would have had a reasonable expectation of success in [the] expression of genes transfected into T-cells." Paper No. 31, page 3, lines 21-22.

Finally, the Examiner concludes:

> One of ordinary skill in the art at the time the invention was made would have been motivated to select and substitute T-cell specific antibodies or gp120 (for the transferrin molecule of Wu et al. or Wagner et al.) as the targeting agents for protein-polycation conjugates or complexes of said conjugates additionally containing nucleic acids because such antibodies would allow for the specific direction and introduction of nucleic acid laden conjugates to T-cells for the purpose of introducing foreign DNA into the cells for either therapeutic purposes or for the production of interleukins (as is indicated by the Hirsch reference). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Paper No. 31, page 3, lines 23-34.

B. Appellants' Response

> ***Issue A: Are claims 1, 2, 8, 11-18 and 36, which are directed to protein-polycation conjugates and, more specifically, antibody-polycation conjugates or antibody fragment-polycation conjugates, which are capable of forming soluble complexes with nucleic acids or nucleic acid analogues and the complexes thereof which are absorbed into T-cells, as well as to processes for introducing nucleic acids into cells which express T-cell surface proteins using the complexes, rendered obvious over prior art references which disclose asialoglycoprotein-, transferrin-, hormone- and antibody-polycation conjugates***

that form complexes with DNA and are absorbed into cells, where there is no suggestion to bind a protein, which is capable of binding to a cell surface protein of T-cell lineage, to a polycation for absorption into T-cells?

The art applied by the Examiner provides neither 1) a suggestion or motivation to combine the various references in any combination nor 2) a reasonable expectation of success of obtaining the claimed invention once the references are combined which are both necessary to establish a *prima facie* case of obviousness. *In re Vaeck*, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). The Examiner admits that the primary "references do not teach the use of T-cell specific antibodies for the targeting of polycation-nucleic acid complexes into cells" as indicated above. In other words, the primary references do not teach the *claimed invention*.

One of the primary references, Wu *et al.*, teaches a gene delivery system comprising DNA carrying complexes containing a non-covalently bound ligand conjugated to a foreign gene. This conjugate appears to be formed by binding receptor-specific ligands such as asialoglycoproteins to polycations. Wu *et al.* make no specific reference to a targeting agent for use against cells of the T-cell lineage, as in the claimed invention. At best, there is no more than an indefinite suggestion to use any ligand, e.g., an antibody, other than the asialoglycoprotein. In effect, Wu *et al.* may disclose a potentially infinite genus of antibodies, although not the antibodies required for the claimed invention, i.e., those capable of binding to a cell surface protein expressed by T-cells.

Wu *et al.'s* description of a ligand conjugated with a foreign gene leaves open to speculation many different possibilities concerning what specifically forms the ligand. As noted by the U.S. Court of Appeals for the Federal Circuit in *In re Baird,* 29 U.S.P.Q.2d 1550, 1552 (1994), a "disclosure of millions of compounds does not render obvious a claim to three

compounds, particularly when that disclosure indicates a *preference* leading away from the claimed compounds." (Emphasis added). A single mention of antibodies can be said to represent a disclosure of more than "millions of compounds." Furthermore, Wu *et al.* clearly exhibit a "preference leading away from the claimed compounds" at column 6, lines 3-5, wherein Wu *et al.* recite, "*[t]ypically* glycoproteins having certain exposed terminal carbohydrate groups are used." (Emphasis added). Moreover, neither the claimed protein-polycation complex nor antibodies used in the claimed complex are *sufficiently similar* in structure to any conjugate or antibody specifically disclosed in Wu *et al.* so as to render the claimed invention obvious. *See In re Jones,* 21 U.S.P.Q.2d 1941, 1943 (Fed. Cir. 1992).

The alternative primary reference, Wagner *et al.*, teaches the use of transferrin-polycation conjugates for nucleic acid delivery into cells containing transferrin receptors. Wagner *et al.* specifically refer to this delivery system as *transferrinfection.* In particular, at page 3414, right hand column, Wagner *et al.* state that, "we have developed a DNA transfection protocol . . . in which we *subvert* a natural iron-uptake mechanism to transport DNA." (Emphasis added). Thus, Wagner *et al.* indicate that DNA uptake occurs by subversion of the natural iron uptake mechanism which exploits the ubiquitous expression of the transferrin receptor on cells. Clearly, such a mechanism must only apply to the use of transferrin and would not suggest a more general approach for targeting protein-polycation complexes as the Examiner contends.

Moreover, nowhere in Wagner *et al.* is there a suggestion that the transferrin-polycation conjugate might be modified such that a protein capable of binding to a T-cell surface receptor might replace the transferrin in the conjugate. Simply because Wagner *et al.* may teach that a polycation such as polylysine or protamine might be attached to transferrin, this is insufficient to

suggest the conjugate of the claimed invention. In any event, the claimed invention specifically excludes conjugates comprising proteins which bind to the transferrin receptor.

Regarding one of the secondary references, Goers *et al.*, the Examiner has failed to point out the manner in which the reference contemplates conjugates comprising proteins which bind to T-cells or how the reference in combination with Wagner *et al.* or Wu *et al.* and Knapp *et al.*, Carriere *et al.* and Young *et al.* or Weinberger *et al.* renders the claimed invention obvious. Goers *et al.* teach therapeutic agent-linker-antibody conjugates. In particular, Goers *et al.* teach DNA-linker-antibody conjugates. *See* column 19, lines 46-54.

Goers *et al.* describe the advantages of DNA-linker-antibody conjugates at column 29, line 31, through column 30, line 5. Particularly, Goers *et al.* indicate that, "the therapeutic agent will act on tumor cells that do *not* possess the antigenic determinant . . . . The entire process is *not* dependant upon internalization of the conjugate." Column 30, lines 2-5 (emphasis added). This is completely contrary to the claimed invention wherein the nucleic acid-protein-polycation complex is internalized into cells which express a T-cell surface protein.

Further, Goers *et al.* rely on the chemical linker in the conjugate to "allow the resulting antibody conjugate to retain the ability to bind antigen and to active the complement cascade." Column 29, lines 33-36. Thus, to modify the Goers *et al.* conjugate so that it resembles the claimed conjugate, the skilled artisan would have to remove the essential chemical linker. In other words, the skilled artisan would have to proceed contrary to the teachings of Goers *et al.*

The Examiner cannot reconstruct the invention by picking and choosing isolated teachings from the prior art. These teachings must be considered as a whole. Goers *et al.* fail to remedy the defects of Wu *et al.* or Wagner *et al.* and actually teach away from the claimed invention by requiring the presence of a chemical linker in the conjugate.

Similarly, the alternative secondary reference, Hirsch *et al.*, fails to remedy the defects of the primary references. Hirsch *et al.* teach the use of a DNA-antibody conjugate with a direct covalent link between the DNA and the antibody. *See* column 2, lines 15-20. Particular antibodies include those against T-cells, i.e., $CD3^+$ cells. Column 2, lines 52-54. The conjugates are used to integrate foreign DNA into cells. Contrary to this, the claimed conjugates are complexed to the DNA by the polycation. Thus, the Hirsch *et al.* conjugate is distinct from the claimed conjugate. Hirsch *et al.* fail to motivate one of ordinary skill in the art to conjugate a T-cell targeting protein to a polycation and complex this conjugate with a nucleic acid. To do so, the skilled artisan would have to proceed contrary to the teachings of Hirsch *et al.*

The Examiner next refers to Knapp *et al.* However, the reliance on Knapp *et al.* is unclear. In Paper No. 22, page 2, lines 34-35, the Examiner states that Knapp *et al.* disclose a variety of T cell-specific antibodies which are commercially available. The Examiner then describes the Carriere *et al.* reference which, contrary to the Examiner's assertions, analyzes the redistribution of surface antigens, such as CD4, following the binding of antibody-gold conjugates to cells, and directs the skilled artisan to the use of ligand-gold conjugates. *See* Carriere *et al.*, page 125, sixth full paragraph, stating that the study "validates the use of ligand-gold conjugates." Knapp *et al.* and Carriere *et al.* do not provide the motivation to use antibodies in conjugates and complexes, such as those claimed, for applications such as transporting nucleic acids into cells. Therefore, Knapp *et al.* and Carriere *et al.* either alone or in combination with the primary and secondary references cited fail to render the claimed invention obvious.

Despite the complete lack of suggestion to combine Knapp *et al.* and Carriere *et al.* with Wu *et al.* or Wagner *et al.* and Goers *et al.* or Hirsch *et al.*, the Examiner concludes that the

"substitution of such antibodies as targeting agents of protein-polycation complexes would have ben [sic] obvious to one of ordinary skill where the targeting of [a] T-cell was desired." Paper No. 31, pages 2-3, bridging paragraph. This is a mere conclusory argument and fails to provide any motivation within the references for the Examiner to substitute such antibodies for the protein of the claimed conjugates and complexes which is not limited to an antibody and which specifically targets T-cells. Simply suggesting that a recitation to T cell-specific antibodies would suggest the claimed invention is insufficient. A motivation must be provided.

The Young *et al.* and Weinberger *et al.* references fail to add anything to the previously applied combination of art. The two references are not analogous to the claimed invention or the other references cited since they do not disclose protein-polycation conjugates or even any type of conjugate. The references describe the transfection of DNA into T-cells. Weinberger *et al.*, an abstract, does not describe the specific method of transfection. Young *et al.* teach that transfection occurs via vectors, not conjugates. Thus, Young *et al.* and Weinberger *et al.*, directed to DNA transfection and silent on the issue of conjugates, do not remedy the defects of Wu *et al.* or Wagner *et al.* in view of Goers *et al.* or Hirsch *et al.*, Carriere *et al.* and Knapp *et al.*

The Examiner contends that pieces of the claimed invention are found in the cited references, however, this is insufficient to obtain the claimed invention and provides nothing more than an "invitation to try" numerous different possible combinations. At best, the Examiner is using an inappropriate "obvious to try" standard. *See In re O'Farrell*, 7 U.S.P.Q.2d 1673, 1681 (Fed. Cir. 1988). The Examiner has failed to point out any teaching in the art which would suggest to one skilled in the art which variables are critical or which would provide guidance leading to appropriate changes necessary to obtain the claimed invention. As a result, one skilled in the art would have *no* direction concerning how to successfully obtain the claimed invention. Contrary

to the Examiner's viewpoint, simply because a piece of art, by itself, may allegedly teach *any* conjugate or *any* type of targeting system, this fails to render the claimed invention obvious.

Overall, the Examiner has picked and chosen individual characteristics of the claimed invention from each piece of the applied art, yet he has failed to provide any argument concerning what the motivation (as found in the cited references) might be for combining the references. By picking and choosing individual teachings of the references and then trying to put these teachings together to arrive at the claimed invention, the Examiner is taking each of the applied references out of context. Simply because the Examiner feels that some of the individual components of the invention might be found in several different pieces of art, this does not in any way suggest the selective combination of these elements to achieve the claimed invention.

The Court of Appeals for the Federal Circuit clearly stated that:

> What we stressed in *Kimberly-Clarke*, and have repeated many times since, was that 35 U.S.C. § 103 requires analysis of a claimed invention as a whole . . . . What must be found obvious to defeat the patent is the claimed composition.
>
> Focusing on the obviousness of substitutions and differences, instead of on the invention as a whole, is a legally improper way to simplify the often difficult determination of obviousness.

The Gillette Company v. S.C. Johnson & Son, Inc., 16 U.S.P.Q.2d 1923, 1927 (Fed. Cir. 1990).

While the cited references may recite some of the characteristics of the claimed invention, they do not suggest the selective combination of such characteristics to produce the protein-polycation conjugates that form complexes with nucleic acids and are capable of binding to a cell surface protein expressed by cells of the T-cell lineage. In other words, the likelihood of successfully obtaining the claimed invention by combining the references is extremely low especially in the absence of any indication concerning the appropriate direction in which to

proceed. As such, the applied art does not establish a *prima facie* basis for rejection under 35 U.S.C. § 103.

Appellant's position is supported in *Ex parte Obukowicz*, 27 U.S.P.Q.2d 1063 (BPAI 1992), wherein the Board reversed an Examiner's rejection under 35 U.S.C. § 103 that was based on a combination of references. In reversing the Examiner's rejection, the Board noted that, "[w]e are unable to find a suggestion [in the art] . . . *to do* what appellants have done." *Id.* at 1065 (emphasis in the original). The Board reviewed the art relied on by the Examiner and dismissed one reference stating that it was "replete with advice" but contained "little information regarding how to use the transformed bacteria and clearly does not specifically suggest appellants' use." *Id.* Appellants respectfully assert that the same could be said for the art cited in the above-captioned application. As in *Obukowicz*, none of the currently cited art is concerned with Appellants' invention, i.e., protein-polycation conjugates and nucleic acid complexes targeted to T-cells. As in *Obukowicz*, none of the art contains the specific suggestion to obtain a protein-polycation conjugate comprising a protein capable of binding to a cell surface protein, other than the transferrin receptor, expressed by cells of the T-cell lineage. Further, as in *Obukowicz*, the cited art gives at best, no more than general guidance and is not *specific* as to the particular form of the claimed invention or how to achieve it.

Appellant's position is further supported by *In re Grabiak*, 226 U.S.P.Q. 870 (Fed. Cir. 1985), wherein the court held that the Examiner had not presented a *prima facie* case of obviousness because the prior art did not suggest that one of ordinary skill in the art could substitute an oxygen atom for the sulfur atom in the claimed compound. According to the court, the "mere fact that it is *possible* to find two isolated disclosures which might be combined in such a way to produce a new compound does not necessarily render such production obvious unless the

art also contains something to suggest the desirability of the proposed combination." *Id.* at 872 (emphasis in the original) (quoting *In re Bergel*, 130 U.S.P.Q. 206, 208 (CCPA 1961)).

Therefore, because the art does not suggest the particular form of the invention, and because the art does not specifically suggest that the skilled artisan do what Appellants have done, Appellants respectfully assert that no motivation exists for combining the cited art and no *prima facie* case of obviousness has been established.

Issue B: Is claim 3, which is directed to CD4-binding protein-polycation conjugates which are capable of binding to CD4 and forming soluble complexes with nucleic acids or nucleic acid analogues which are absorbed into T-cells, rendered obvious over prior art references which disclose asialoglycoprotein-, transferrin-, hormone- and antibody-polycation conjugates that form complexes with DNA and are absorbed into cells, where there is no suggestion to bind a CD4-binding protein to a polycation for absorption into T-cells?

Applicants reiterate and incorporate by reference the arguments presented above with respect to Issue A. It should be noted that claim 3 is directed to a specific protein component of the protein-polycation conjugates defined in claim 1. There is no suggestion in the references cited to substitute the specific CD4-binding protein required by claim 3 for the proteins of Wagner *et al.* or Wu *et al.* Carriere *et al.* do refer to CD4 surface antigens on T-cells, however, as noted above, Carriere *et al.* teach antibody-gold conjugates. The reference fails to teach a CD4-binding protein-polycation conjugate and fails to provide motivation to bind a CD4-binding protein to a polycation.

Issue C: Is claim 4, which is directed to conjugates containing a polycation bound to an anti-CD4 monoclonal antibody or conjugates containing a polycation bound to an anti-CD4 monoclonal antibody fragment containing a gp120 binding epitope which are capable of forming soluble complexes with nucleic acids or nucleic acid analogues which are absorbed into T-cells, rendered obvious over prior art references which disclose asialoglycoprotein-, transferrin-, hormone- and antibody-polycation conjugates that form complexes with DNA and are absorbed into cells, where there is no suggestion to bind an anti-CD4 antibody monoclonal or anti-CD4 monoclonal antibody fragment containing a gp120 binding epitope to a polycation for absorption into T-cells?

Applicants reiterate and incorporate by reference the arguments presented above with respect to Issue A. It should be noted that claim 4 is directed to a specific protein component of the protein-polycation conjugates defined in claim 1. There is no suggestion in the references cited to substitute the anti-CD4 monoclonal antibody required by claim 4 for the proteins of Wagner *et al.* or Wu *et al.* Carriere *et al.* do refer to CD4 surface antigens on T-cells, however, as noted above, Carriere *et al.* teach antibody-gold conjugates. The reference fails to teach an anti-CD4 monoclonal antibody-polycation conjugate and fails to provide motivation to bind an anti-CD4 monoclonal antibody to a polycation.

Issue D: Is claim 5, which is directed to conjugates containing a polycation bound to HIV-1 gp120, conjugates containing a polycation bound to an HIV-1 gp120 homologous protein of a related retrovirus or conjugates containing a polycation bound to a CD4-binding fragment of an HIV-1 gp120 homologous protein of a related retrovirus, which are capable of forming soluble complexes with nucleic acids or nucleic acid analogues which are absorbed into T-cells, rendered obvious over prior art references which disclose asialoglycoprotein-, transferrin-, hormone- and antibody-polycation conjugates that form complexes with DNA and are absorbed into cells, where there is no suggestion to bind HIV-1 gp120, a homologous protein of a related retrovirus or a CD4-binding protein fragment thereof to a polycation for absorption into T-cells?

Applicants reiterate and incorporate by reference the arguments presented above with respect to Issue A. It should be noted that claim 5 is directed to a specific protein component of

the protein-polycation conjugates defined in claim 1. There is no suggestion in the references cited to substitute HIV-1 gp120 required by claim 5 for the proteins of Wagner *et al.* or Wu *et al.*

Issue E: Is claim 6, which is directed to protein-polycation conjugates wherein the protein binds to a tumor marker expressed on T-cells, which are capable of forming soluble complexes with nucleic acids or nucleic acid analogues which are absorbed into T-cells, rendered obvious over prior art references which disclose asialoglycoprotein-, transferrin-, hormone- and antibody-polycation conjugates that form complexes with DNA and are absorbed into cells, where there is no suggestion to bind a tumor marker-binding protein to a polycation for absorption into T-cells?

Applicants reiterate and incorporate by reference the arguments presented above with respect to Issue A. It should be noted that claim 6 is directed to a specific protein component of the protein-polycation conjugates defined in claim 1. There is no suggestion in the references cited to substitute the specific tumor marker-binding protein required by claim 6 for the proteins of Wagner *et al.* or Wu *et al.* Carriere *et al.* do refer to CD7 surface antigens, i.e., tumor markers, on T-cells, however, as noted above, Carriere *et al.* teach antibody-gold conjugates. The reference fails to teach the combination of a tumor marker-binding protein and a polycation and fails to provide motivation to bind a tumor maker-binding protein to a polycation.

Issue F: Is claim 7, which is directed to CD7-binding protein-polycation conjugates, which are capable of forming soluble complexes with nucleic acids or nucleic acid analogues which are absorbed into T-cells, rendered obvious over prior art references which disclose asialoglycoprotein-, transferrin-, hormone- and antibody-polycation conjugates that form complexes with DNA and are absorbed into cells, where there is no suggestion to bind a CD7-binding protein to a polycation for absorption into T-cells?

Applicants reiterate and incorporate by reference the arguments presented above with respect to Issue A. It should be noted that claim 7 is directed to a specific protein component of

the protein-polycation conjugates defined in claim 1. There is no suggestion in the references cited to substitute the specific CD7-binding protein required by claim 7 for the proteins of Wagner *et al.* or Wu *et al.* Carriere *et al.* do refer to CD7 surface antigens on T-cells, however, as noted above, Carriere *et al.* teach antibody-gold conjugates. The reference fails to teach a CD7-binding protein-polycation conjugate and fails to provide motivation to bind a CD7-binding protein to a polycation.

Issue G: Is claim 19, which is directed to complexes comprising protein-polycation conjugates bound to nucleic acids, wherein the complexes contain an additional non-covalently bound polycation and are absorbed into T-cells, rendered obvious over prior art references which disclose asialoglycoprotein-, transferrin-, hormone- and antibody-polycation conjugates that form complexes with DNA and are absorbed into cells, where there is no suggestion to bind a second polycation to the conjugate?

Applicants reiterate and incorporate by reference the arguments presented above with respect to Issue A. It should be noted that claim 19 is directed to a specific protein-polycation-nucleic acid complex as more generally defined in claim 17. There is no suggestion in the references cited to bind a second polycation to the Wagner *et al.* or Wu *et al.* protein-polycation conjugates.

Issue H: Is claim 20, which is directed to complexes comprising protein-polycation conjugates bound to virus-inhibiting nucleic acids, which are absorbed into T-cells, rendered obvious over prior art references which disclose asialoglycoprotein-, transferrin-, hormone- and antibody-polycation conjugates that form complexes with DNA and are absorbed into cells, where there is no suggestion to bind a virus-inhibiting nucleic acid to a protein-polycation conjugate for absorption into T-cells?

Applicants reiterate and incorporate by reference the arguments presented above with respect to Issue A. It should be noted that claim 20 is directed to a specific nucleic acid component of the protein-polycation-nucleic acid complexes defined in claim 17. There is no suggestion in the references cited to substitute the specific virus-inhibiting nucleic acid required by claim 20 for the DNA of Wagner *et al.* or Wu *et al.*

Issue I: Is claim 37, which is directed to a process for introducing nucleic acids into T-cells wherein antibody-protein A-protamine-virus-inhibiting nucleic acid complexes are absorbed into T-cells, rendered obvious over prior art references which disclose asialoglycoprotein-, transferrin-, hormone- and antibody-polycation conjugates that form complexes with DNA and are absorbed into cells, where there is no suggestion to combine an antibody, protein A, protamine and a virus-inhibiting nucleic acid for absorption into T-cells?

Applicants reiterate and incorporate by reference the arguments presented above with respect to Issue A. It should be noted that claim 37 is directed to a process for nucleic acid introduction into T-cells wherein a conjugate containing an antibody directed against a T-cell surface protein is combined with protein A, a virus-inhibiting nucleic acid and protamine. There is no suggestion in the references cited to substitute the specific conjugate components required by claim 37 for the protein-polycation conjugates and DNA of Wagner *et al.* or Wu *et al.*

Issue J: Is claim 38, which is directed to pharmaceutical preparations containing protein-polycation conjugates bound to therapeutically or gene therapeutically active nucleic acids to form complexes which are absorbed into T-cells, rendered obvious over prior art references which disclose asialoglycoprotein-, transferrin-, hormone- and antibody-polycation conjugates that form complexes with DNA and are absorbed into cells, where there is no suggestion to bind a therapeutically or gene therapeutically active nucleic acid to a protein-polycation conjugate for absorption into T-cells?

Applicants reiterate and incorporate by reference the arguments presented above with respect to Issue A. It should be noted that claim 38 is directed to pharmaceutical preparations containing the protein-polycation conjugates defined in claim 17 that form complexes with specific nucleic acids. There is no suggestion in the references cited to substitute the specific nucleic acid required by claim 38 for the DNA of Wagner *et al.* or Wu *et al.*

Issue K: Are claims 39 and 40, which are directed to anti-CD3 monoclonal antibody-polycation conjugates (claim 39) which are capable of forming soluble complexes with nucleic acids or nucleic acid analogues, and the complexes thereof (claim 40), which are absorbed into T-cells, rendered obvious over prior art references which disclose asialoglycoprotein-, transferrin-, hormone- and antibody-polycation conjugates that form complexes with DNA and are absorbed into cells, where there is no suggestion to bind an anti-CD3 monoclonal antibody to a polycation for absorption into T-cells?

Applicants reiterate and incorporate by reference the arguments presented above with respect to Issue A. It should be noted that claims 39 and 40 require specific protein components of the protein-polycation conjugates and complexes defined in claims 1 and 17, respectively. There is no suggestion in the references cited to substitute the specific anti-CD3 antibodies required by claims 39 and 40 for the proteins of Wagner *et al.* or Wu *et al.* As indicated above, Hirsch *et al.* teach conjugates containing DNA bound to an anti-CD3 antibody wherein there is a direct covalent link between the DNA and the antibody. However, the Hirsch *et al.* conjugate is distinct from the claimed conjugate wherein the DNA is complexed to the polycation. Hirsch *et al.* fail to provide the motivation to conjugate a T-cell targeting protein to a polycation and complex this conjugate with a nucleic acid.

II. Rejection of claims 17, 20, 28, 29 and 32-34 under 35 U.S.C. § 103

A. Examiner's Statement of Rejection

The Examiner has maintained the rejection of claims 17, 20, 28, 29 and 32-34 under 35 U.S.C. § 103. Specifically, the Examiner set forth the rejection as follows:

> Claims 17, 20, 28-29 and 32-34 stand rejected under 35 U.S.C. § 103 as being unpatentable over Wu et al. (AC1) or Wagner et al. (AT2) in view of Goers et al., Hirsch et al. ('132), Knapp et al., and Carriere et al., as applied above and further in view of Haseloff et al., or Rossi et al. ('019) and Applicants' admitted prior art regarding oncogene inhibitory nucleic acids (see page 26, paragraph 3 of the specification).

Paper No. 31, page 6, lines 22-27.

The Examiner indicates that Wu *et al.*, Wagner *et al.*, Goers *et al.* and Hirsch *et al.* are cited for the same reasons set forth in the first rejection under 35 U.S.C. § 103. According to the Examiner, the two primary references do not teach "the use of antibody targeting agents and nucleic acids comprising ribozymes." Paper No. 31, page 6, lines 33-34. To make up for the deficiencies of the primary references, the Examiner cites Haseloff *et al.* stating that this reference teaches the existence of ribozymes and indicates that ribozymes have a variety of uses including targeting a gene RNA transcript.

As an alternative to Haseloff *et al.*, the Examiner cites Rossi *et al.* asserting that this reference teaches that ribozymes "provide a basis for gene therapy of various diseases, including HIV infection" and further teaches that transfection and transformation techniques, whereby genes encoding ribozymes are introduced into cells, are known, and that ribozymes can be used to inactivate endogenous RNA transcripts produced by certain oncogenes. Paper No. 31, page 6, line 38, through page 7, line 9.

Based on the alleged teachings of Haseloff *et al.* or Rossi *et al.* in combination with the references previously cited, the Examiner concludes:

> [O]ne of ordinary skill would have recognized that the targeting of ribozymes to T-cells expressing oncogene proteins or HIV proteins using polycation-protein conjugates . . . would have been useful for inactivation of the genetic transcripts contained within the cells. Further, one of ordinary skill would have recognized . . . that the targeting specificity of the system disclosed by Wagner et al. could be greatly enhanced by the use of antibodies to specifically target therapeutic agents such as ribozymes.
>
> One of ordinary skill in the art . . . would have been motivated to select and substitute T-cell specific antibodies or gp120 . . . as the targeting agents for protein-polycation conjugates or complexes of said conjugates additionally containing nucleic acids because such antibodies would allow for the specific direction and introduction of ribozyme laden conjugates to T-cells for the purpose of introducing foreign nucleic acids, such as ribozymes, into the cells for the inactivation of RNA contained with [sic] the cells . . . . Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Paper No. 31, page 7, lines 11-30.

B. Appellants' Response

> ***Issue A(1): Is claim 17, which is directed to complexes comprising protein-polycation conjugates bound to nucleic acids which are absorbed into T-cells, rendered obvious over prior art references which disclose asialoglycoprotein-, transferrin-, hormone- and antibody-polycation conjugates that form complexes with DNA and are absorbed into cells, where there is no suggestion to bind a protein, which is capable of binding to a cell surface protein of T-cell lineage, to a polycation for absorption into T-cells?***

The art applied by the Examiner provides neither 1) a suggestion or motivation to combine the various references in any combination nor 2) a reasonable expectation of success of obtaining

the claimed invention once the references are combined which are both necessary to establish a *prima facie* case of obviousness. *In re Vaeck*, 20 U.S.P.Q. 1438, 1442 (Fed. Cir. 1991). The Examiner admits that the references do not teach "the use of T cell-specific antibodies for the targeting of polycation-nucleic acid complexes into cells" or the combination of targeting agents and ribozymes. Paper No. 31, page 2, lines 28-29, and page 6, lines 33-34, respectively. In other words, the references do not teach the *claimed invention*. Further, the cited art fails to suggest using ribozymes as part of *any* protein-polycation conjugate.

Appellants have already discussed Wu *et al.*, Wagner *et al.*, Goers *et al.*, Hirsch *et al.*, Knapp *et al.* and Carrier *et al.* in the first rejection under 35 U.S.C. § 103. Appellants maintain that the same arguments apply to the Examiner's reliance on that art in this rejection and reiterate that the combination of Wu *et al.* or Wagner *et al.* in view of Goers *et al.* or Hirsch *et al.* and Knapp *et al.* and Carrier *et al.* fails to render obvious any aspect of the claimed invention.

In the second rejection under 35 U.S.C. § 103, the Examiner additionally cites Haseloff *et al.* to illustrate that ribozymes are known to have variety of applications. Regardless of whether Haseloff *et al.* teach ribozymes or even applications for these molecules, Haseloff *et al.* clearly fail to provide any suggestion whatsoever to complex a ribozyme to a protein-polycation conjugate. Thus, Haseloff *et al.* do not bring one any closer to obtaining the claimed invention. Simply because a piece of art may describe ribozymes and how ribozymes *per se* may be used, this in no way suggests using ribozymes as part of a protein-polycation conjugate as in the claimed invention.

The Examiner contends that Haseloff *et al.* indicate that ribozymes could be inserted into a variety of genetic constructs, however, this still fails to suggest the claimed invention. Merely being able to insert a ribozyme into a genetic construct does not render the claimed invention obvious. One cannot insert ribozymes into just *any* genetic construct to arrive at the claimed

invention. Rather, the ribozymes must comprise part of a specific protein-polycation conjugate. Further, there must be some reason to insert a ribozyme into the protein-polycation conjugate required to arrive at the claimed invention. Such a reason does not exist in the cited art.

The Examiner next contends that Rossi *et al.* provide a variety of therapeutic applications for ribozymes. A "variety of therapeutic applications" does not suggest incorporating a ribozyme into a protein-polycation conjugate as required by claim 17. To imply that such is the case would suggest that Rossi *et al.* render obvious virtually any use, whatsoever, of ribozymes in a therapeutic regime. This would certainly be stretching the Rossi *et al.* disclosure. The Examiner fails to provide any evidence that Rossi *et al.* suggest the use of ribozymes in the specific construction of polycation-protein conjugates. Simply because one can or may be able to do something does not mean that the claimed invention is obvious. Further, Rossi *et al.* fail to make any suggestion regarding the targeting of ribozymes to specific cell types using a cell specific targeting mechanism. Thus, even if the Examiner attempts to buttress his argument by claiming that Rossi *et al.* address the issue of cell transfection using ribozymes, this still fails to remedy the previous defects. Merely using ribozymes in *any* cell transfection system is not the claimed invention. Rather a specific protein-polycation conjugate also comprising a ribozyme is necessary.

Either alone or in combination, Haseloff *et al.* and Rossi *et al.* fail to remedy the defects of the initial combination. The use of Haseloff *et al.* and Rossi *et al.* is nothing more than an attempt to add components previously missing from the combination in an attempt to arrive at the claimed invention. As argued above, picking and choosing pieces from the art, without any suggestion or motivation to do so, is an improper approach to the obviousness analysis. The motivation to combine references must be present before combining the art, not after one has already decided what they wish the combination to show.

Issue L: ***Is claim 28, which is directed to complexes comprising protein-polycation conjugates bound to virus-inhibiting nucleic acids in the form of ribozymes, which are absorbed into T-cells, rendered obvious over prior art references which disclose asialoglycoprotein-, transferrin-, hormone- and antibody-polycation conjugates that form complexes with DNA and are absorbed into cells and which disclose that ribozymes are known, where there is no suggestion to bind a specific ribozyme to a protein-polycation conjugate for absorption into T-cells?***

Applicants reiterate and incorporate by reference the arguments presented above. It should be noted that claim 28 is directed to a specific nucleic acid component in the form of a ribozyme of the protein-polycation-nucleic acid conjugates defined in claim 17. There is no suggestion in the references cited to substitute the specific virus-inhibiting nucleic acid in ribozyme form required by claim 28 for the DNA of Wagner *et al.* or Wu *et al.* Haseloff *et al.* and Rossi *et al.* do mention that ribozymes could be inserted into a genetic construct or used in a cell transfection system. However, merely being able to insert a ribozyme into a genetic construct or in a cell transfection system does not render the claimed invention obvious. Rather, the ribozymes must comprise part of a specific protein-polycation conjugate which is simply not taught by the cited references.

Issue M: ***Is claim 29, which is directed to complexes comprising protein-polycation conjugates bound to virus-inhibiting nucleic acids in the form of genetic units consisting of tRNA-genes as carrier genes and ribozyme genes, which are absorbed into T-cells, rendered obvious over prior art references which disclose asialoglycoprotein-, transferrin-, hormone- and antibody-polycation conjugates that form complexes with DNA and are absorbed into cells, and which disclose that ribozymes are known, where there is no suggestion to bind the genetic unit to a protein-polycation conjugate for absorption into T-cells?***

Applicants reiterate and incorporate by reference the arguments presented above. It should be noted that claim 29 is directed to a specific nucleic acid component in the form of a genetic unit consisting of a tRNA gene and a ribozyme gene of the protein-polycation-nucleic acid complexes

defined in claim 17. There is no suggestion in the references cited to substitute the specific virus-inhibiting nucleic acid in the genetic unit form required by claim 29 for the DNA of Wagner *et al.* or Wu *et al.* Haseloff *et al.* and Rossi *et al.* do mention that ribozymes could be inserted into a genetic construct or used in a cell transfection system. However, merely being able to insert a ribozyme into a genetic construct or in a cell transfection system does not render the claimed invention obvious. Rather, the ribozymes must comprise part of a specific protein-polycation conjugate which is simply not taught by the cited references.

> ***Issue N: Is claim 32, which is directed to complexes comprising protein-polycation conjugates bound to oncogene-inhibiting nucleic acids, which are absorbed into T-cells, rendered obvious over prior art references which disclose asialoglycoprotein-, transferrin-, hormone- and antibody-polycation conjugates that form complexes with DNA and are absorbed into cells, where there is no suggestion to bind an oncogene-inhibiting nucleic acid to a protein-polycation conjugate for absorption into T-cells?***

Applicants reiterate and incorporate by reference the arguments presented above. It should be noted that claim 32 is directed to a specific nucleic acid component of the protein-polycation-nucleic acid complexes defined in claim 17. There is no suggestion in the references cited to substitute the specific oncogene-inhibiting nucleic acid required by claim 32 for the DNA of Wagner *et al.* or Wu *et al.*

> ***Issue O: Are claims 33 and 34, which are directed to complexes comprising protein-polycation conjugates bound to oncogene-inhibiting nucleic acids in the form of ribozymes, which are absorbed into T-cells, rendered obvious over prior art references which disclose asialoglycoprotein-, transferrin-, hormone- and antibody-polycation conjugates that form complexes with DNA and are absorbed into cells and which disclose that ribozymes are known, where there is no suggestion to bind a ribozyme to a protein-polycation conjugate for absorption into T-cells?***

Applicants reiterate and incorporate by reference the arguments presented above. It should be noted that claims 33 and 34 are directed to a specific nucleic acid component in the form of a ribozyme of the protein-polycation-nucleic acid complexes defined in claim 17. There is no suggestion in the references cited to substitute the specific oncogene-inhibiting nucleic acid in the ribozyme form required by claims 33 and 34 for the DNA of Wagner *et al.* or Wu *et al.* Haseloff *et al.* and Rossi *et al.* do mention that ribozymes could be inserted into a genetic construct or used in a cell transfection system. However, merely being able to insert a ribozyme into a genetic construct or in a cell transfection system does not render the claimed invention obvious. Rather, the ribozymes must comprise part of a specific protein-polycation conjugate which is simply not taught by the cited references.

III. Rejection of claims 1, 9 and 10 under 35 U.S.C. § 103

A. Examiner's Statement of Rejection

The Examiner has rejected claims 1, 9 and 10 under 35 U.S.C. § 103. Specifically, the Examiner set forth the rejection as follows:

> Claims 1 and 9-10 are rejected under 35 U.S.C. § 103 as being unpatentable over Wu et al. (AC1) or Wagner et al. (AT2) in view of Goers et al. and Knapp et al. and Calliere [sic] et al., as applied above . . . and further in view of Goding et al., Ghetie et al. (Mol. Immunol., 23:1371), Ghetie et al. (Mol. Immunol., 25:473), or Mota et al. (Immunol. Letters).

Paper No. 31, page 8, lines 20-24.

The Examiner indicates that Wu *et al.*, Wagner *et al.*, Goers *et al.*, Knapp *et al.* and Carriere *et al.* are cited for the same reasons set forth in the previous rejections under 35 U.S.C.

§ 103. According to the Examiner, these references do not teach "the binding attachment of polycation to antibody through a protein A-antibody interaction." Paper No. 31, page 8, lines 27-28. To make up for the deficiencies of Wu *et al.*, Wagner *et al.*, Goers *et al.*, Knapp *et al.* and Carriere *et al.*, the Examiner cites Goding *et al.*, Ghetie *et al.* (vol. 23), Ghetie *et al.* (vol. 25) and Mota *et al.*

According to the Examiner, Goding *et al.* teach that protein A can be an immunological reagent "for the attachment of reagents to antibody molecules." Paper No. 31, page 8, line 30. Specifically, Goding *et al.* allegedly teach that one can attach labels such as fluorescein to antibodies bound to cells through protein A-antibody interactions. Based on this assessment, the Examiner surmises that "it would have been obvious to one of ordinary skill in the art that polycations could also be attached to antibodies through the protein A-antibody interaction, thereby providing a means of attaching DNA to antibodies or facilitate [sic] the isolation of antibodies through ion exchange chromatography." Paper No. 31, page 8, lines 34-38.

Regarding the Ghetie *et al.* references and the Mota *et al.* reference, the Examiner asserts that the references teach that the skilled artisan would recognize the utility of protein A conjugates as "universal" agents which could be attached to any antibody. The Examiner concludes:

> One of ordinary skill in the art at the time the invention was made would have been motivated to select make [sic] an antibody-protein A-polycation compound because such proteins would have allowed for the specific direction and introduction of nucleic acid laden conjugates to T-cells or facilitated the isolation of such antibodies through ion exchange chromatography. From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Paper No. 31, page 9, lines 3-11.

B. Appellants' Response

Issue A(2): Is claim 1, which is directed to protein-polycation conjugates which are capable of forming soluble complexes with nucleic acids or nucleic acid analogues which are absorbed into T-cells, rendered obvious over prior art references which disclose asialoglycoprotein-, transferrin-, hormone- and antibody-polycation conjugates that form complexes with DNA and are absorbed into cells, where there is no suggestion to bind a protein, which is capable of binding to a cell surface protein of T-cell lineage, to a polycation for absorption into T-cells?

The art applied by the Examiner provides neither 1) a suggestion or motivation to combine the various references in any combination nor 2) a reasonable expectation of success of obtaining the claimed invention once the references are combined which are both necessary to establish a *prima facie* case of obviousness. *In re Vaeck*, 20 U.S.P.Q. 1438, 1442 (Fed. Cir. 1991). Further, the cited art fails to suggest incorporating protein A into any polycation-containing conjugate.

Appellants have already discussed Wu *et al.*, Wagner *et al.*, Goers *et al.*, Carriere *et al.* and Knapp *et al.* in the first rejection under 35 U.S.C. § 103, and maintain that the same arguments apply to the Examiner's reliance on that art in this rejection. Appellants reiterate that the combination of Wu *et al.*, Wagner *et al.*, Goers *et al.*, Carriere *et al.* and Knapp *et al.* fails to render obvious any aspect of the claimed invention. The references do not teach binding a polycation and an antibody through a protein A link as admitted by the Examiner in Paper No. 18, page 8, lines 5-8. In addition, the references do not teach binding protein A to a polycation.

In the third rejection under 35 U.S.C. § 103, the Examiner additionally cites Goding *et al.*, Ghetie *et al.* (vol. 23), Ghetie *et al.* (vol. 25) and Mota *et al.* These four references add nothing to the already rebutted combination of art that would remedy the deficiencies in the art. Goding *et al.* do nothing more than provide general information on the use of protein A as an

immunological reagent. Thus, the reference fails to provide the missing motivation to incorporate protein A into a polycation-containing conjugate.

The remaining three references relate to protein A-ricin conjugates, not protein A-polycation conjugates for the transfer and subsequent internalization of nucleic acids into T-cells. Further, both Ghetie *et al.* references and the Mota *et al.* reference relate to the binding of protein A-ricin conjugates to "antibody coated cells." This is clearly distinct from the claimed protein A-polycation conjugates and antibody-protein A-polycation conjugates.

Additionally, the term "universal" does not refer to a universal agent for attachment to antibodies of any specificity as asserted by the Examiner in Paper No. 31, pages 8-9, bridging sentence. The reference to a "universal" reagent in Ghetie *et al.* (vol. 23) is to the "use of protein A-ricin toxin conjugate as a 'universal' specific toxin for the '*in vitro*' killing of various antibody-coated target cells" provided that a *Staphylococcus* protein-A reacting antitarget antibody is present. Ghetie *et al.* (vol. 23), last two lines of the abstract, and page 1378.

Either alone or in combination, Goding *et al.*, Ghetie *et al.* (vol. 23), Ghetie *et al.* (vol. 25) and Mota *et al.* fail to remedy the defects of the initial combination. Further, the use of any one of these four references is nothing more than an attempt to add components previously missing from the combination in an attempt to arrive at the claimed invention. As argued above, picking and choosing pieces from the art, without any suggestion or motivation to do so, is an improper approach to the obviousness analysis. The motivation to combine references must be present before combining the art, not after one has already decided what they wish the combination to show.

Issue P: ***Is claim 9, which is directed to antibody-protein A-polycation conjugates which are capable of forming soluble complexes with nucleic acids or nucleic acid analogues which are absorbed into T-cells, rendered obvious over prior art references which disclose asialoglycoprotein-, transferrin-, hormone- and antibody-polycation conjugates that form complexes with DNA and are absorbed into cells and which disclose that protein A is known, where there is no suggestion to bind an antibody-protein A complex to a polycation for absorption into T-cells?***

Applicants reiterate and incorporate by reference the arguments presented above. It should be noted that claim 9 is directed to a specific protein component of the protein-polycation conjugates defined in claim 1. There is no suggestion in the references cited to substitute the antibody bound to protein A required by claim 9 for the proteins of Wagner *et al.* or Wu *et al.* Goding *et al.* do nothing more than provide general information on the use of protein A as an immunological reagent and Ghetie *et al.* (vol. 23), Ghetie *et al.* (vol. 25) and Mota *et al.* only relate to protein A-ricin conjugates, not protein A-polycation conjugates for the transfer and subsequent internalization of nucleic acids into T-cells. Thus, the references fail to provide the missing motivation to incorporate protein A into a polycation-containing conjugate

Issue Q: ***Is claim 10, which is directed to protein A-polycation conjugates which may be used to prepare antibody-protein A-polycation conjugates which are capable of forming soluble complexes with nucleic acids or nucleic acid analogues which are absorbed into T-cells, rendered obvious over prior art references which disclose asialoglycoprotein-, transferrin-, hormone- and antibody-polycation conjugates that form complexes with DNA and are absorbed into cells and which disclose that protein A is known, where there is no suggestion to bind protein A to a polycation?***

Applicants reiterate and incorporate by reference the arguments presented above. It should be noted that claim 10 is directed to a specific type of conjugate. There is no suggestion in the references cited to bind protein A to the Wagner *et al.* or Wu *et al.* polycations to obtain a protein

A-polycation conjugate as required by claim 10. Goding *et al.* do nothing more than provide general information on the use of protein A as an immunological reagent and Ghetie *et al.* (vol. 23), Ghetie *et al.* (vol. 25) and Mota *et al.* only relate to protein A-ricin conjugates, not protein A-polycation conjugates for the transfer and subsequent internalization of nucleic acids into T-cells. Thus, the references fail to provide the missing motivation to incorporate protein A into a polycation-containing conjugate

Summary

Appellants have shown that the present invention is not obvious over the references cited by the Examiner. Accordingly, the Honorable Board is respectfully requested to reverse the Examiner's final rejection of claims 1-20, 28, 29, 32-34 and 36-40 under 35 U.S.C. § 103 and remand this application for issuance.

Respectfully submitted,

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Appendix of the Claims[1]

1. New protein-polycation conjugates which are capable of forming, with nucleic acids or nucleic acid analogues, soluble complexes which are absorbed into human or animal cells, characterised in that the protein component of the conjugates is a protein capable of binding to a cell surface protein other than the transferrin receptor expressed by cells of the T-cell lineage, so that the complexes formed are taken up into cells which express the T-cell surface protein.

2. Conjugates according to claim 1, characterised in that their protein component is a preferably monoclonal antibody or a fragment thereof, directed against the T-cell surface protein.

3. Conjugates according to claim 1 or 2, characterised in that they contain a protein capable of binding to CD4.

4. Conjugates according to claim 3, characterised in that they contain a monoclonal anti-CD4 antibody or the fragment thereof which contains a gp120 binding epitope.

5. Conjugates according to claim 3, characterised in that they contain as protein HIV-1 gp120 or a homologous protein of related retroviruses or a fragment thereof which binds to CD4.

6. Conjugates according to claim 1 or 2, characterised in that they contain a protein which binds to a tumour marker expressed on T-cells.

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[1]Appellants have submitted an Amendment Under 37 C.F.R. § 1.116 together with the Appeal Brief. If this Amendment is entered, claim 34 will be canceled.

7. Conjugates according to claim 6, characterised in that they contain a protein which binds to CD7.

8. Conjugates according to claim 2, characterised in that they contain an antibody in a form which is directly coupled to the polycation.

9. Conjugates according to claim 2, characterised in that they contain an antibody in a form bound by means of a protein A coupled to polycation.

10. Protein A-polycation conjugates for preparing antibody conjugates according to claim 9.

11. Conjugates according to claim 1, characterised in that the polycation is an optionally modified protamine.

12. Conjugates according to claim 1, characterised in that the polycation is an optionally modified histone.

13. Conjugates according to claim 1, characterised in that the polycation is a synthetic homologous or heterologous polypeptide.

14. Conjugates according to claim 13, characterised in that the polypeptide is polylysine.

15. Conjugates according to claim 11, characterised in that the polycation has about 20 to 500 positive charges.

16. Conjugates according to claim 11, characterised in that the molar ratio of T-cell binding protein to polycation is about 10:1 to 1:10.

17. New protein-polycation/nucleic acid complexes which are absorbed into human or animal cells, characterised in that the protein component of the conjugates is a protein capable of binding to a cell surface protein other than the transferrin receptor expressed by cells of the T-cell lineage, so that the complexes formed are taken up in cells which express the T-cell surface protein.

18. Complexes according to claim 17, characterised in that they contain as the conjugate component one of the conjugates defined in claim 1.

19. Complexes according to claim 17, characterised in that they additionally contain a non-covalently bound polycation, which may optionally be identical to the polycation of the conjugate, so that the internalisation and/or expression of the nucleic acid achieved by the conjugate is increased.

20. Complexes according to claim 17, characterised in that they contain a virus inhibiting nucleic acid.

28. Complexes according to claim 20, characterised in that they contain an inhibiting nucleic acid in the form of a ribozyme, optionally together with a carrier RNA, or the gene coding therefor.

29. Complexes according to claim 28, characterised in that they contain a nucleic acid in the form of a genetic unit consisting of a tRNA-gene as carrier gene and a ribozyme gene arranged within this gene.

32. Complexes according to claim 17, characterised in that they contain an oncogene-inhibiting nucleic acid.

33. Complexes according to claim 32, characterised in that they contain an oncogene-inhibiting nucleic acid in the form of a ribozyme, optionally together with a carrier RNA or the gene coding therefor.

34. Complexes according to claim 33, characterised in that they contain an oncogene-inhibiting nucleic acid in the form of a ribozyme, optionally together with a carrier RNA, or the gene coding therefor.

36. Process for introducing nucleic acid or acids into cells which express a T-cell surface protein, by forming one of the complexes defined in claim 17, which is preferably soluble under physiological conditions, from one of the protein-polycation conjugates defined in claim 1 and nucleic acid or acids, optionally in the presence of non-covalently bound polycation, and

bringing cells which express the T-cell surface protein, especially T-cells, into contact with this complex, optionally under conditions under which the breakdown of nucleic acid in the cell is inhibited.

37. Process for introducing nucleic acid or acids into cells which express a T-cell surface protein, in which a complex is formed from a protein A-polycation conjugate, consisting of protein A and one of the polycations defined in claim 11 and one of the nucleic acids defined in claim 20, and the complex is brought into contact, in the presence of an antibody directed against a T-cell surface protein, with cells which express this surface protein, the antibody being bound to the conjugate component of the complex.

38. Pharmaceutical preparation containing as active component one or more therapeutically or gene therapeutically active nucleic acids in the form of one of the complexes defined in claim 17.

39. Conjugates according to claim 1, characterized in that said protein is an anti-CD3 monoclonal antibody.

40. Complexes according to claim 17, characterized in that said protein is an anti-CD3 monoclonal antibody.